## REMARKS

This application has been amended in a manner that is believed to place in condition for allowance.

Claims 1-19 have been canceled. Claims 20-39 have been added.

Claims 20-23 are directed to a method for increasing gene transfer efficiency and a gene transfer immediate by an adeno-associated virus factor. Support for the claims may be found in original claim 7 and in paragraph [0075] of the published application for this application (i.e., U.S. 2008/0214446).

Support for claims 21-25 may be found in original claim 8 and in paragraph [0048] of the published application.

Claim 26 is supported by paragraph [0046] of the published application.

Support for claims 27-29 may be found in original claim 9 and in paragraphs [0051], [0056] of the published application.

Claims 30 and 31 are supported by original claims 9-11 and paragraphs [0051], [0057] of the published application.

Claims 36-39 are directed to a method for increasing the efficiency of a transduction mediated by an adeno-associated virus vector (AAV). Support for the claims may be found in original claim 7 and in paragraph [0075] of the published application for this application.

Claims 1-19 have been canceled without prejudice and/or disclaimer.

Applicants amend page 21 of the specification in view of a translation and Certificate of Translation submitted with this response.

Applicants respectfully submit that no new matter has been added to the disclosure.

Claims 4-6, 10, 11, and 15-19 were objected to under 37 C.F.R 1.75 (c) as allegedly being in improper form because they have multiple dependent claim cannot depend from another multiply dependent claim. Applicants respectfully submit that the present Amendment overcomes this objection.

Claims 1-19 have been canceled. Claims 20-39 have been drafted without any multiple dependencies.

Claim 3 was objected to under 37 C.F.R. 1.75 (c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. As noted above, claim 3 has been canceled. Thus, applicants respectfully request that this objection be withdrawn.

Claims 12-14 were rejected under 35 U.S.C. 101 for reciting a "use". Applicants believe that the present amendment overcomes this rejection.

As noted above, claims 12-14 have been canceled. New claims 20-39 are directed to method claims. Thus, the new claims have been drafted in a manner so as to avoid this issue.

Claims 12-14 were rejected under 35 U.S.C. 112, second paragraph, for allegedly being indefinite. Applicants respectfully submit that the present amendment overcomes this rejection.

As noted above, claims 12-14 has been canceled. None of the pending claims are directed to "use" claims. New claims 20-39 are directed to method

claims. Thus, the new claims have been drafted in a manner so as to avoid this issue.

Claims 1-3 and 7-9 were rejected under 35 U.S.C. 102 (a) as allegedly being anticipated by GOLDSMITH. This rejection is traversed.

Applicants respectfully submit that GOLDSMITH fails to qualify as prior art. The present application claims priority to Japanese Application JP2003-122968. Applicants submit herewith a verified translation of this application. As this application claims priority to an application having a priority date before the publication date of GOLDSMITH, Applicants respectfully submit that GOLDSMITH fails to qualify as prior art.

Applicants respectfully request that the anticipation rejection be withdrawn.

Claims 1-3 and 7-9 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by JUNG. This rejection is traversed.

As noted above, claims 1-3 and 7-9 have been canceled. Claims 1-3 were directed to an enhancer composition. As the new claims are directed to a method, applicants respectfully submit that this aspect of the rejection is moot in view of the pending claims.

JUNG discloses that inhibitors of histone deacetylase (HDACis) induce hyperacetylation in chromatin resulting in the activation of certain genes. Histone deacetylation activity is recruited by co-repressor proteins to certain regions of the chromatin. Aberrant histone acetylation caused by that recruitment is suspected of resulting in pathogenesis of certain cancers on that level (abstract).

However, JUNG neither discloses nor suggests that an adeno-associated viral genome can undergo histone modification immediately after an infection. In this regard, JUNG fails to anticipate the claimed invention, which is directed to a method for increasing gene transfer or transduction efficiency in a gene transfer or transduction mediated by an adeno-associated virus vector.

Thus, JUNG does not discuss a method for increasing gene transfer or transduction efficiency in a gene transfer or transduction mediated by an adeno-associated virus vector, as claimed.

JUNG cannot inherently anticipate the claimed invention. The Examiner is respectfully reminded of the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted) (The claims were drawn to a disposable diaper having three fastening elements. The reference disclosed two fastening elements that could

perform the same function as the three fastening elements in the claims. The court construed the claims to require three separate elements and held that the reference did not disclose a separate third fastening element, either expressly or inherently.). Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species. With no recognition of utilizing an adeno-associated viral genome as claimed, it cannot be said that this missing subject matter is necessarily present.

In view of the above, applicants respectfully request that the rejection be withdrawn.

Claims 1, 3, 7 and 9 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by KWON. Applicants respectfully submit that the present amendment overcomes this rejection.

Claims 1-3 were directed to an enhancer composition. As the new claims are directed to a method, Applicants respectfully submit that this aspect of the rejection is moot in view of the pending claims.

Applicants respectfully submit that at best the disclosure of KWON is cumulative to JUNG. KWON disclose that a histone deacetylation inhibitor FK228 inhibits tumor angiogenesis (abstract).

KWON neither discloses nor suggests a method for increasing gene transfer or transduction efficiency in a gene transfer or transduction mediated by an adeno-associated virus vector.

In this regard, applicants respectfully submit that KWON fails to anticipate the claimed invention for the same reasons as JUNG.

Claims 1 and 3 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by CHEN. Applicants respectfully submit that present amendment overcomes this rejection.

As noted above, claims 1 and 3 were directed to an enhancer composition. The pending claims are directed to a method. Accordingly, applicants respectfully request that the rejection be withdrawn.

Claims 1-3 were rejected under 35 U.S.C. 102 (b) as allegedly being anticipated by KITAZONO.

Claims 1-3 were directed to an enhancer composition. However, applicants respectfully note that the pending claims are directed to a method.

In this regard, applicants respectfully request that the anticipation rejection be withdrawn.

Claims 7-9 were rejected under 35 U.S.C. 103 (a) as allegedly being unpatentable over KITAZONO. Applicants respectfully submit that the present amendment overcomes this rejection.

The claimed invention is directed to a method that utilizes an adeno-associated viral vector. KITAZONO is drawn to an adenovirus vector. KITAZONO does not disclose or suggest that an episomal adeno-associated viral genome, which has undergone chromosomal integration, can undergo histone modification to enhance its gene expression.

Although KITAZONO indicates that strain FR901228 increased CAR and $\alpha_v$ integrin RNA levels (the 4th line from the bottom, left column, p6329), CAR is a receptor of adenovirus, not adeno-associated virus. Indeed, KITAZONO points out that the addition of HDACis after an adenovirus infection is known to may increase expression of viral proteins and transgene expression (see page 6329, right column, 4th line from the bottom, right column, p6329). As chromatin in cells is histone modified, it was known that HDACis enhance the acetylation of histone-associated chromatin in cells. This results in the enhancement of certain gene expression in cells (see JUNG, KWON). An episomal adeno-associated viral genome or nucleotide sequence is a foreign gene which does not originally exist in cells, it was not known that an adeno-associated viral genome could undergo histone modification immediately after infection.

In this regard, KITAZONO fails to anticipate or render obvious the claimed invention. One skilled in the art would have lacked the motivation to modify KITAZONO in a manner that would have resulted in the claimed invention.

Applicants respectfully submit that claims 22, 24 and 39 are even further distinguishable from the claimed invention. KITAZONO plainly fails to disclose or suggest a method of "administering....simultaneously with, immediately before or

immediately after AAV-vector-mediated gene transfer". In the adenovirus-mediated gene transfer method suggested in KITAZONO, an HDACi needs to be administered before adenovirus infection to increase CAR and $\alpha_V$ integrin RNA levels.

However, the inventors of the present application were the first to discover that adeno-associated virus mediated transduction efficiency peaked when cells were treated with an HDACi at the time of virus transduction in the case of a single administration of the HDACi. In this regard, the Examiner's attention is respectfully directed to the article Okada et al., Mol. Ther. 13: 738-746, 2006.

Applicants respectfully submit that the article provides further evidence as to the nonobviousness of the claimed invention.

Fig. 1 (D) of Okada et al. shows that cells treated with FR901228 simultaneously with recombinant adeno-associated viral infection had a hundreds-fold increase in AAV-mediated gene expression (Okada et al., Mol. Ther. 13: 738-746, 2006; Fig1-D: from about 0 of NC to about 45 at 0h), while KITAZONO indicates that cells treated with FR901228 prior to adenovirus infection had only a 4-10-fold increase in transgene expression (the 4$^{th}$ line from the bottom, abstract; the 7$^{th}$ line from the bottom, left column, p6329). In this regard, Applicants respectfully request the claimed invention exhibits unexpected results.

The Examiner is respectfully reminded that the Patent Office must consider objective indicia of nonobviousness whenever present. Specifically, the Patent Office is bound to consider evidence of unexpected results, commercial success, long-felt but unresolved needs, failure of others, skepticism of experts. *Stratoflex,*

*Inc. v. Aeroquip Corp.*, 713 f. 2d 1530, 1538 (Fed Cir. 1983). Federal Circuit precedent mandates consideration of comparative data in the specification which is intended to illustrated the claimed invention in reaching a conclusion with regard to the obviousness of the claims. *In re Margolis*, 785 F. 2d 1029 (Fed Cir. 1986). (Vacating Board decision which refused to consider data in the specification which compared an embodiment of the invention with the prior art product and noting that such evidence spoke to unexpected results and non-obviousness).

Applicants respectfully request that the rejection be withdrawn.

In view of the present amendment and foregoing remarks, therefore, applicants believe that the present application is in condition for allowance at the time of the next official action. Allowance and passage to issue on that basis is respectfully requested.

Respectfully submitted,

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APPENDIX:

The Appendix includes the following items:

- OKADA et al., Mol. Ther. 13:738-746, 2006
- Certificate of Translation